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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/478,977	01/06/00	BROOKS	P 13761-727

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/478,977	Applicant(s) BROOKS ET AL.	
	Examiner Alana M. Harris, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-18,20-25,27-30,32-34,36-38 and 40-64* is/are pending in the application.

4a) Of the above claim(s) *20-25,27-30,32-34,36-38 and 40-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-4 and 6-18 with denatured collagen type-I as the species) in Paper No. 13, filed August 20, 2001 is acknowledged. The traversal is on the ground(s) that the Examiner did not recognize the proper relationship between the claim groups, hence the restriction between Groups I and II is not proper. This is found unpersuasive.

The Examiner does acknowledge the inadvertent error in the restriction requirement set forth in Paper No. 10, mailed June 21, 2001. The claims encompass a product and the process of using and not an apparatus and the product made as noted in Paper No. 10. Notwithstanding, Groups I and II are separate groups encompassing a product and method, respectively. A restriction/election exemplifying such is set forth in the following paragraphs.

The requirement is still deemed proper and is therefore made FINAL. However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

2. I. Claims 1-4, 6-18, drawn to an antagonist that specifically binds to a denatured collagen or collagens, classified in class 530, subclass 350.

II. Claims 20-25, 27-30, 32-34, 36-38, 40-42 and 60-64, drawn to a method of inhibiting angiogenesis comprising administering an antagonist to a tissue, classified in class 514, subclass 1.

III. Claims 43-55, drawn to a method for screening for denatured collagen antagonists comprising providing a putative antagonist, classified in class 435, subclass 7.1.

IV. Claims 56-59, drawn to a peptide, classified in class 530, subclass 300.

3. The inventions are distinct, each from the other because of the following reasons:

Groups I and IV are structurally and functionally different products which are made by different methods and have different uses. The examination of all groups would require different searches in the U.S. Patent Shoes and the scientific literature and would require the consideration of different patentability issues.

The methods of Groups II and III differ in the method objectives, method steps and parameters in the reagents used.

4. Inventions of Group I and Groups II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product of Group I can use any of the method of Groups II or III.

Inventions of Group IV and Groups II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a

materially different process of using that product (MPEP § 806.05(h)). In the instant case the product of Group IV can use any of the method of Groups II or III.

5. This application contains claims directed to the following patentably distinct species of the claimed invention: antagonists that specifically bind to structurally different collagens of Group I (claims 1-4 and 6-18) and method Group III (claims 43-55). If Applicants elects any one of Groups I or III they must elect one of the five different types of collagen to be used with an antagonists and in the different methods which have different endpoints:

A. Denatured collagen type-I,
B. Denatured collagen type-II,
C. Denatured collagen type-III,
D. Denatured collagen type-IV, or
E. Denatured collagen type-V

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, the claims listed in Groups I and III are generic.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

7. Claims 1-4, 6-18, 20-25, 27-30, 32-34, 36-38 and 40-64 are pending.

Claims 1, 11, 20-23, 27-30, 32-34, 36-38, 40-43 and 56 have been amended.

Claims 20-25, 27-30, 32-34, 36-38 and 40-64, drawn to non-elected inventions are withdrawn from examination.

Claims 1-4 and 6-18 are examined on the merits.

Priority

8. The instant application is granted the effective filing date of January 6, 2000. The provisional documents 60/114,877 (filed January 6, 1999), 60/114,878 (filed January 6, 1999), 60/152,496 (filed September 2, 1999) and 60/143,534 (filed July 13, 1999) from which Applicant requests priority benefit were unavailable. Once these documents become available to the Examiner they will be reviewed and the priority date of the instant application will be reestablished if warranted.

Oath/Declaration

9. The Examiner has acknowledged Applicants' claim for priority to provisional applications under 35 U.S.C. 119 (e) on the first line of the specification. However, the instant declaration does not list any of the four provisional applications listed in paragraph number 8. The instant declaration does not acknowledge the filing of any provisional applications. A new oath or declaration is required in the body of which the present application should be identified by application number and filing date.

Drawings

10. The drawings are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

Claim Objections

11. Claims 6, 8 and 9 are objected to because of the following informality: they contain reference to non-elected species not examined on the merits. Correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 11 is are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of antibodies HU177, HUVIV26 and XL313. It is not clear that antibodies possessing the identical properties of these instant antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for generating and isolating the specified monoclonal antibodies, this method will not necessarily reproduce antibodies and which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to screen all of the possible antibody species to obtain the claimed antibodies.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibodies, a suitable deposit of the molecules designated as HU177, HUIV26 and XL313 for patent purposes, evidence of public availability of the claimed cell lines or evidence of the reproducibility without undue experimentation of the claimed cell lines, is required.

Applicants have not made a referral to the deposit of the antibodies in the specification. There is insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the

grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

14. Claims 1-4 and 6-18 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the antagonists, designated monoclonal antibodies, HU177, HUIV26 and XL313 for the inhibition of angiogenesis, does not reasonably provide enablement for a host of antagonists, such as an oligonucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants' specification contains examples and figures that provide evidence that monoclonal antibodies, HU177, HUIV26 and XL313 are capable of inhibiting angiogenesis. This enabling disclosure provides evidence only of the specified antagonists capable of arresting angiogenesis. Applicants have not provided any evidence that suggests that other monoclonal antibodies or oligonucleotides would have the same inhibitory effect. A number of antibodies may possess a high affinity for the denatured collagens but not be effective in inhibiting angiogenesis. One of ordinary skill in the art could screen for effective antibody antagonists, but that would be burdensome considering the number of antibodies that possibly bind denatured collagen, type I. The specification only discloses three monoclonal antibodies effective in inhibiting

angiogenesis and does not disclose any oligonucleotides effective in inhibiting angiogenesis. Applicants' claims are not commensurate in scope with what is enabled within the specification.

It would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the infinite number of antagonists that could possibly inhibit angiogenesis.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-4 and 6-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation "denatured collagen" in claims 1 and 6-9 is vague and indefinite. It is not clear by what means the collagen was denatured. For example was the collagen chemically or structurally denatured? Accordingly, the metes and bound of the claims cannot be determined.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-4, 6-8, 10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellon (Analytical Biochemistry 150:188-202, 1985/ IDS reference C1). Bellon teaches collagen type I digested with cyanogen bromide (CNBr), see abstract and column 1 of page 188. Both monoclonal and polyclonal antibodies bound these denatured collagenous proteins (see page 189, column 1, bridging paragraph). As indicated in column 2, first full paragraph, page 188 the method implemented by Bellon could not be used on whole-tissue samples because of insolubility of the collagens. These whole-tissue sample invariably contain native triple helical forms of collagen, type I. Intrinsically, these antibodies would bind the native triple helical form of the collagen type I with substantially reduced affinity, from 3 fold lower to 10 fold lower than that for denatured collagen.

Bellon does not teach an antagonist, wherein the said antagonist inhibits angiogenesis. However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the antibodies of Bellon to a subject with angiogenesis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Bellon. As suggested on page 201, column 1 the technique taught has a number of potential uses such as detection and quantification of collagens in a number of diseases. Those antibodies used in Bellon's method could also be considered therapeutic in the inhibition of angiogenesis.

19. Claims 1-4, 6-8, 10, 12-14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellon (Analytical Biochemistry 150:188-202, 1985/ IDS reference C1), in view of U.S. Patent Number 5,693,762 (filed June 7, 1995). The teachings of Bellon have been discussed above a preceding paragraph. Bellon does not teach an antibody that is humanized or chemically modified.

However, U.S. Patent #5,693,762 does teach a method of humanizing antibodies by which the donor immunoglobulin is converted into a human-like immunoglobulin by combining it complementarity determining regions (CDR's) with a human framework, as well as teach the other forms of immunoglobulins such as Fv and Fab fragments. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the teachings of both, Bellon and the patent. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies of Bellon and fragments of such because these design antibodies are capable of specifically react with strong affinity to a predetermined antigen, as well as they are easily and economically produced in a manner suitable for therapeutic formulation.

20. Claims 1-4, 6-8, 10, 12-14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellon (Analytical Biochemistry 150:188-202, 1985/ IDS reference C1), in view of European Patent 0 510 949 A2 (October 28, 1992). The teachings of Bellon have been discussed above. Bellon does not teach an antibody that is conjugated to a cytotoxic or cytostatic agent.

However, Pouletty teaches methods for the preparation of antibody-cytokine fusion protein moieties for use in immunotherapeutic treatment methods. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the cytokine immunoconjugates, taught in Pouletty, in order to create a therapeutic antagonist for the inhibition of angiogenesis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Pouletty, that such cytokine/antibody conjugates effectively destroy the targeted cell population (see abstract).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Alana M. Harris, Ph.D.
September 29, 2001

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